UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/926,554	11/19/2001	Enrico Di Salle	215164US0PCT	8709

20306 7590 07/28/2003

MCDONNELL BOEHNEN HULBERT & BERGHOFF
300 SOUTH WACKER DRIVE
SUITE 3200
CHICAGO, IL 60606

EXAMINER	
JIANG, SHAOJIA A	
ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 07/28/2003

10

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/926,554	Applicant(s) SALLE ET AL.	
	Examiner Shaojia A Jiang	Art Unit 1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

This application is a national stage entry of PCT/EP00/03407 International Filing Date: 04/14/2000, which claims priority to GB 9911582.6.

Election/Restrictions

Applicant's election with traverse of the invention of species, anthracycline compounds as the anti-neoplastic agents in Paper No. 9, submitted May 9, 2003 is acknowledged. However, it is noted that anthracycline compounds are considered to be a genus, and Applicant has not elected the species for aromatase inhibitor. Thus, Applicant's election of species is not a specified combination of individual active compounds. Nonetheless, on consideration by the examiner, the specie election requirement is modified to include all anti-neoplastic agents and all aromatase inhibitor recited in the claims herein as a single specie.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 24-34 and 36-47 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant's preliminary amendment with respect to newly submitted claims 24-34 and 36-47 has been fully considered but is deemed to insert new matter into the claims, since the specification and claims as originally filed fail to provide the support for the negative limitation, "the aromatase inhibitor is not aminoglutheimide". Consequently, there is nothing within the instant specification which would lead the artisan in the field to believe that Applicant was in possession of the invention as it is now claimed.

Any negative limitation or exclusionary proviso must have basis in the original disclosure. See Ex parte Grasselli, 231 USPQ 393 (Bd. App. 1983), aff 'd mem., 738 F.2d 453 (Fed. Cir. 1984). The mere absence of a positive recitation is not basis for an exclusion. Any claim containing a negative limitation which does not have basis in the original disclosure should be rejected under 35 U.S.C. 112, first paragraph as failing to comply with the written description requirement. See MPEP § 2163 - § 2163.07(b) for a discussion of the written description requirement of 35 U.S.C. 112, first paragraph.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 24-26, 29, 34-38, 41, and 46 are rejected under 35 U.S.C. 112, first paragraph, for scope of enablement because the specification, while being enabling for the particular antineoplastic agents disclosed in claim 27 for example, in combination with the particular aromatase inhibitors disclosed in the last two lines of claim 25 for

example, in compositions and methods herein, does not reasonably provide enablement for any compounds having antineoplastic function and any compounds for inhibiting aromatase, recited in the claims herein. Moreover, the specification does not reasonably provide enablement for the combinations of any compounds having these recited functions producing superadditive antitumor effects.

The recitations, antineoplastic agents, antineoplastic topoisomerase II inhibitors, antineoplastic antimicrotubule agents, antineoplastic alkylating, agents antineoplastic antimetabolites, and antineoplastic topoisomerase I inhibitors, and aromatase inhibitors, are seen to be merely functional language.

The instant specification fails to provide information that would allow the skilled artisan to fully practice the instant invention without ***undue experimentation***. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

The nature of the invention: The instant invention pertains to compositions and methods for treating breast cancer in humans.

The relative skill of those in the art: The relative skill of those in the art is high.

The breadth of the claims: The instant claims are deemed very broad since these claims reads on any of antineoplastic agents, antineoplastic topoisomerase II inhibitors, antineoplastic antimicrotubule agents, antineoplastic alkylating, agents antineoplastic antimetabolites, and antineoplastic topoisomerase I inhibitors, and aromatase inhibitors employed in the compositions and methods for the particular treatment herein.

The amount of direction or guidance presented:

Functional language at the point of novelty, as herein employed by Applicants, is admonished in *University of California v. Eli Lilly and Co.* 43 USPQ2d 1398 (CAFC, 1997) at 1406: stating this usage does "little more than outline goal appellants hope the recited invention achieves and the problems the invention will hopefully ameliorate". The CAFC further clearly states that "[A] written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula, [or] chemical name, of the claimed subject matter sufficient to distinguish it from other materials" at 1405(emphasis added), and that "It does not define any structural features commonly possessed by members of the genus that distinguish from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus.." at 1406 (emphasis added).

In the instant case, antineoplastic agents, antineoplastic topoisomerase II inhibitors, antineoplastic antimicrotubule agents, antineoplastic alkylating, agents antineoplastic antimetabolites, and antineoplastic topoisomerase I inhibitors, and

aromatase inhibitors, recited in the instant claims are purely functional distinction. Hence, these functional recitations read on any compounds that might have the recited functions. However, the specification merely provides particular compound for each kind of functional compounds for the compositions and methods.

Thus, Applicants functional language at the points of novelty fails to meet the requirements set forth under 35 U.S.C. 112, first paragraph. Claims employing functional language at the exact point of novelty, such as Applicants', neither provide those elements required to practice the inventions, nor "inform the public during the life of the patent of the limited of monopoly asserted" (*General Electric Company v. Wabash Appliance Corporation et al.* 37 USPQ at 468 (US Supreme Court 1938)).
The predictability or unpredictability: the instant claimed invention is highly *unpredictable* as discussed below:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instant claimed invention is highly unpredictable since one skilled in the art cannot fully described genus, visualize or recognize the identity of the members of the genus, by structure, formula, or chemical name, of the claimed subject matter, as discussed above in *University of California v. Eli Lilly and Co.* Hence, in the absence of fully recognizing the identity of the members genus herein, one of skill in the art would

be unable to fully predict possible physiological activities of any compounds having claimed functional properties in the pharmaceutical compositions herein.

Moreover, one of skill in the art would recognize that it is highly unpredictable in regard to therapeutic effects, side effects, and especially serious toxicity that may be generated by drug-drug interactions when and/or after administering to a host (e.g., a male) the ***combination*** of any compounds represented by antineoplastic agents, antineoplastic topoisomerase II inhibitors, antineoplastic antimicrotubule agents, antineoplastic alkylating, agents antineoplastic antimetabolites, and antineoplastic topoisomerase I inhibitors, and aromatase inhibitors, which may encompass more than a thousand compounds. See text book "Goodman & Gilman's The Pharmacological Basis of Therapeutics" regarding possible drug-drug interactions (9th ed, 1996) page 51 in particular. This book teaches that "The frequency of significant beneficial or adverse drug interactions is unknown" (see the bottom of the left column of page 51) and that "Recognition of beneficial effects and recognition of and prevention of adverse drug interactions require a thorough knowledge of the intended and possible effects of drugs that are prescribed" and that "The most important adverse drug-drug interactions occur with drugs that have serious toxicity and a low therapeutic index, such that relatively small changes in drug level can have significant adverse consequences" (see the right column of page 51) (emphases added). In the instant case, in the absence of fully recognizing the identity of the members genus herein, one of skill in the art would not be able to fully predict possible adverse drug-drug interactions occurring with many combinations of any compounds having claimed functional properties in the

pharmaceutical compositions herein to be administered to a host. Thus, the teachings of the book clearly support that the instant claimed invention is highly unpredictable.

The presence or absence of working examples and the quantity of experimentation necessary:

It is noted that only one particular aromatase inhibitor, exemestane in combination with epirubicin or docetaxel, two particular antineoplastic agents, were tested in the working examples in the specification (see page 8-9 of specification). Thus, the evidence in the examples is also not commensurate in scope with the claimed invention and does not demonstrate criticality of a claimed range of any of compounds having the recited functional properties in the claimed compositions and method and producing superadditive antitumor effects. See MPEP § 716.02(d).

Thus, the specification fails to provide sufficient support of the broad use of any compounds having those functions recited in the instant claims. As a result, necessitating one of skill to perform an exhaustive search for the embodiments of any compounds having those functions recited in the instant claims suitable to practice the claimed invention.

Genentech, 108 F.3d at 1366, states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the *Wands* factors, the case *University of California v. Eli Lilly and Co.* (CAFC, 1997) and *In re Fisher* (CCPA 1970) discussed above, to practice

the claimed invention herein, a person of skill in the art would have to engage in *undue experimentation* to test all compounds encompassed in the instant claims and their combinations employed in the claimed compositions to be administered to a host, with no assurance of success.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 25, 27, 31, 34, 37, 39, 44-45, and 47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 25, 27, 37, and 39 contain the trademark/trade name YM 511, PNU 159548, and PNU 166148. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade names are used to identify/describe particular agents or compounds herein and, accordingly, the identification/description is indefinite.

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claims 44-45 recite the broad recitation "one or two antineoplastic agents and the steroidal aromatase inhibitors" and the claims also recites "exemestane" and fadrozole" in claim 44, and "exemestane" and "formestane" in claim 45, which are the narrower statements of the range/limitation.

Claims 31 and 47 recite the limitation "an effective antineoplastic amount of vinblastine" for example, and other particular antineoplastic agents. There is insufficient antecedent basis for this limitation in the claim since claims 24 and 40 do not recite these particular agents.

Claim 34 recites the limitation "wherein said product is capable of ..." which renders the claim indefinite since it is unclear which "said product" is represented in the claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 24-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Grem et al. (PTO-1449 submitted March 7, 2002) and Tognella et al. (4,871,528, PTO-892) and Shashoua et al. (5,795,909 PTO-892).

Grem et al. discloses that the combination chemotherapy with cyclophosphamide, doxorubicin and 5-fluorouracil, which are the instant claimed antineoplastic agents, and further in combination with the particular aromatase inhibitor, aminogluthetimide, are useful in a composition and a method of treating breast cancer in humans. See abstract, the right column of page 528, and the entire article).

Tognella et al. discloses that the known anti-tumor agents, cyclophosphamide, methotrexate, etoposide, and 5-fluorouracil, which are the instant claimed antineoplastic agents, alone and in combination with other anti-tumor agents, or in combination with reduced glutathione (GSH), is useful in a composition and a method of treating breast cancer in humans and lowering the side effects in humans caused by breast cancer therapy with anti-tumor agents (antineoplastic agents) (increasing the long term survival rates). See abstract, col. 1 lines 20-38. Tognella et al. also discloses that the instant preferred anthracycline compounds such as doxorubicin, epirubicin, and mitoxanthrone

(see col. lines 50-57). Tognella et al. further discloses the effective amounts of the active agents in a composition to be administered for treating breast cancer in humans to produce synergistic effects (see col.4 lines 21-25 and 42-54, Table at col.5 lines 57-63, Table 1-4 at col.10-12).

Shashoua et al. discloses that the instant preferred antineoplastic agents such as paclliotaxe, docetaxel, edatrexate, epirubicin, 5-fluorouracil, gemcitabine, irinotecan, mitoxantrone and topotecan, and the instant preferred aromatase inhibitors such as anastrozole, fadrozole, letroxole, vorozole and exemestane, are known to be useful in the treatment of cancers, tumors or proliferative disorders including breast cancer (see Fig. 27) and reducing side-effects. See abstract, col.1 lines 45-46 and col.30 line 48 to col.32.

The prior art does not expressly disclose that the employment of the instant preferred antineoplastic agents in combination with the instant preferred aromatase inhibitors in pharmaceutical compositions and methods for treating breast cancer in humans and lowering the side effects in humans. The prior art does also not expressly disclose the effective amounts of active agents in the combination of pharmaceutical compositions herein to be administered.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to employ the instant preferred antineoplastic agents in combination with the instant preferred aromatase inhibitors in pharmaceutical compositions and methods for treating breast cancer in humans and lowering the side

effects in humans, and to optimize the effective amounts of active agents in the composition herein to be administered.

One having ordinary skill in the art at the time the invention was made would have been motivated to employ the instant preferred antineoplastic agents in combination with the instant preferred aromatase inhibitors in pharmaceutical compositions and methods for treating breast cancer in humans and lowering the side effects in humans, since the instant preferred antineoplastic agents and the instant preferred aromatase inhibitors, alone and/or in combination, are known to be useful in pharmaceutical compositions and methods for treating breast cancer in humans and lowering the side effects in humans based on the prior art.

Therefore, one of ordinary skill in the art would have reasonably expected that combining the instant preferred antineoplastic agents and the instant preferred aromatase inhibitors in pharmaceutical compositions to be administered, both known useful for the same purpose, i.e., treating breast cancer, would improve the therapeutic effects for treating the same disorder, and/or would produce additive therapeutic effects in treating the same. See *In re Kerkhoven*, 205 USPQ 1069 (CCPA 1980) regarding combination inventions. It is considered prima facie obvious to combine two active composition components into a single composition to form a third composition useful for the very same purpose; idea of combining them flows logically from their having been individually taught in prior art.

Moreover, the teachings of Grem et al. and Tognella et al. in regard to the combination chemotherapies for breast cancer using the instant agents have also provided the motivation to make the present invention.

Additionally, one of ordinary skill in the art would have been motivated to optimize the effective amounts of active agents in the composition because the optimization of known effective amounts of known active agents to be administered based on the prior art, is considered well within the skill of artisan. It has been held that it is within the skill in the art to select optimal parameters, such as amounts of ingredients, in a composition in order to achieve a beneficial effect. See *In re Boesch*, 205 USPQ 215 (CCPA 1980).

Thus the claimed invention as a whole is clearly prima facie obvious over the combined teachings of the prior art.

In view of the rejections to the pending claims set forth above, no claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Jiang, whose telephone number is (703) 305-1008. The examiner can normally be reached on Monday-Friday from 9:00 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan, Ph.D., can be reached on (703) 305-1877. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 305-1235.

S. Anna Jiang, Ph.D.
Patent Examiner, AU 1617
July 17, 2003